REMARKS

The Office Action and the cited and applied references have been carefully reviewed. No claim is allowed. Claims 1-13 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claims 1-13 have been rejected under 35 U.S.C. §112, first paragraph, because the examiner states that the specification, while being enabling for regulating or reducing the phototoxicity by using certain effector photosensitizers and certain quenching photosensitizer molecule, does not reasonably provide enablement for reducing, regulating or preventing phototoxicity using all effector photosensitizer and all quenching photosensitizer molecules. This rejection is respectfully traversed.

The present invention is not intended to encompass the use of any and all photosynthesizing agents. Rather, it is intended to encompass only pairs of photosensitizers where the effector photosensitizer of the pair results in phototoxicity during photodynamic therapy of a targeted tissue and where the quenching photosensitizer of the pair has an absorption spectrum which falls outside the wavelength range used to excite the effector photosensitizer molecule and quenches any undesirable

phototoxic activity of the effector photosensitizer in neighboring tissue of the tissue targeted for destruction (to avoid collateral phototoxic damage). As taught on page 9, paragraph [0022], tissues that neighbor those singled out for photoablation are protected by loading the neighboring tissues with a quenching photosensitizer that is not sought to be photosensitized.

As acknowledged by the examiner, the skill of those in the art of photosensitizers and photodynamic therapy is high. From the guidance provided in the present specification at pages 9-15 and in the Examples, in particular the preferred embodiment with verteporfin and hypericin for photodynamic therapy, one of skill in the art would be enabled for the scope of the presently claimed invention. For instance, the disclosures and teachings in the instant specification show that a photodynamic agent (photosensitizer), which when photoactivated by light in wavelengths which it absorbs (hypericin at wavelengths of 540-600 nm with peaks at 545 and 590 nm) and in which it causes photodynamic damage, acts differently and becomes a quencher of the photodynamically-generated singlet oxygen and free radicals of another photodynamic agent/photosensitizer (verteporfin) if the photo-excitation wavelengths are in a range absorbed only by verteporfin (a cutoff above 650 nm and a peak of 689 nm). This

would be well understood by those in the art as only occurring if the quenching photosensitizer has a shorter wavelength absorption range (with higher energy-hypericin) than the effector photosensitizer which has a longer absorption range (with lower energy - verteporfin) as energy always flows from high to low and not vice versa.

Once those of skill in the art are in possession of the novel approach in the present application based on the guidance provided therein, they will be readily able to determine with only routine experimentation which pairs of photodynamic agents/photosensitizers would act in the same manner as the verteporfin-hypericin pair for the purposes of photodynamic therapy without collateral damage to neighboring tissue. The experimental results disclosed in the Examples, which are directed to (1) protection of ARPE cells by hypericin from verteporfin-induced phototoxicity, (2) effect of hypericin on intracellular accumulation of verteporfin in ARPE and EH cells, and (3) selective protection of neighboring tissues from collateral phototoxic damage during photosnsitization of tissues targeted from ablation would lead one of skill in the art to reasonably expect that such "competitive quenching" of collateral phototoxic damage to neighboring tissue would work during photodynamic therapy, even in the absence of *in vivo* photodynamic

therapy data. It has been well established that *in vivo* data is not required for enablement.

As those in the art are highly skilled and the art of photodynamic agents/photosensitizers is well developed (many photosensitizers with their absorption ranges are well-known and characterized in the art), only routine experimentation is needed to determine what pairs of photosensitizers would be suitable as an effector and quenching photosensitizer pair.

Accordingly, those of skill in the art are well enabled for the scope of the presently claimed invention. Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1-13 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Medline Abstract 10755329 (Scott et al., 2000) and Margolis-Nunno et al., U.S. Patent 6,087,141. The examiner states that the Medline abstract teaches the use of veteprofin in photodynamic therapy for the treatment of age related macular degeneration. The examiner acknowledges that the above reference differs from the claimed invention in the use of a quenching agent in order to reduce the phototoxicity of an effector photosensitizer molecule. The examiner then holds that Margolis-Nunno et al. teach the addition of a quenching agent such as hypericin to an effector molecule being used as antiviral

agent in blood, for killing viruses without affecting the surrounding functional cells. Margolis-Nunno is also held by the examiner to teach that the invention can be employed to treat the product of the composition containing non-blood normal or cancerous cells or the product of gene splicing. It is the examiner's position that it would have been obvious to a person skilled in the art to incorporate a quenching agent into the teaching of the primary reference, considering that Margolis et al. allegedly teach the use of a quenching agent in photodynamic therapy for the reduction of the phototoxicity of the effector photosensitizing molecule to the functional tissues and cells is old and well known. The examiner asserts that one skilled in the art would have been motivated to combine the teachings of the above references, since one relates to the use of photodynamic therapy for the treatment of the claimed disorders and the other relates to the addition of a quenching agent such as hypericin to photodynamic therapy in order to reduce the phototoxicity of the effector molecule. The examiner further asserts that the use of the quencher compounds for the reduction of the phototoxicity of the surrounding tissues would have been obvious to a person skilled in the art, considering that Margolis et al. allegedly teach that the use of the quenching agents is not only for the

protection of blood cells but it can also be used for non-blood or cancerous cells. This rejection is respectfully traversed.

Even though the examiner has pointed out the disclosure at column 4, lines 54-56 of Margolis-Nunno that the invention can be used to treat the product of a composition containing non-blood normal or cancerous cells or the product of gene splicing, this disclosure is to be taken with the teachings of Margolis-Nunno as a whole. It is quite clear that the crux of Margolis-Nunno's invention is directed to inactivating viruses in a biological composition, such as whole blood, red blood cell concentrates, etc. (column 4, lines 37-45), by UV irradiation with or without irradiation sensitizers or quenchers. This selective inactivation of viruses in the biological composition by Margolis-Nunno serves to preserve labile blood cell functional and structural features (column 6, lines 53-56). As defined by Margolis-Nunno at column 4, lines 46-53, the term "biological composition" or "cell-containing composition" is not to be construed as to include any living organism but is instead intended to be carried out in an *in vitro* embodiment to obtain an *in vitro* produced product.

By contrast, the present invention is intended for administration *in vivo* in a patient where a tissue of the patient is targeted for destruction, not a virus. As taught throughout

the instant specification, the novel feature of the invention is to create differential compartmentalization of a quencher photosensitizer (in the preferred embodiment, hypericin is differentially compartmentalized to the extravascular space) so as to prevent phototoxicity from an effector photosensitizer in the compartment containing the quencher photosensitizer while at the same time not interfering with the beneficial phototoxic effects of the photodynamic therapy in the targeted compartment (i.e., the intravascular compartment in the preferred embodiment). This feature is positively recited in the claims by the language "quenching the activity of the effector photosensitizer molecule in neighboring tissues of the tissue targeted for destruction".

The cited and applied Medline abstract 10755329 of Scott et al. provides merely a disclosure of selective damage by verteporfin therapy to neovascular endothelial cells leading to thrombus formation and specific occlusion of choroidal neovascular vessels in subfoveal lesions in age-related macular degeneration patients. However, there is absolutely no suggestion or motivation in this cited abstract or in the prior art to introduce a quenching photosensitizer into a neighboring tissue/compartment to prevent collateral damage. While the problem of collateral damage was recognized in photodynamic

therapy of age-related macular degeneration, there is simply nothing in the prior art that would suggest or motivate one of ordinary skill in the art to use such differential compartmentalization. Certainly, there is no compartmentalization in Margolis-Nunno as the virus to be inactivated is mixed with the other components of the "biological composition" to be treated by irradiation. The photodynamic "sterilization" process in Margolis-Nunno is performed *in vitro*, not *in vivo* in a patient. Furthermore, the disclosure of hypericin in Margolis-Nunno is as an irradiation sensitizer (see column 5, lines 38-53), not as a quencher compound as alleged by the examiner. Therefore, there is clearly no suggestion or motivation to combine the disclosures of the cited and applied references, without the hindsight of applicant's own disclosure, to lead one of ordinary skill in the art to use two different photosensitizer, one being the effector photosynthesizer and the other being a quenching photosensitizer, with differential compartmentalization to prevent collateral damage to neighboring tissue of the target tissue for photodynamic therapy.

With due respect to the examiner, the examiner has combined unrelated and disparate disclosures from the two cited references, which one of skill in the art would not be motivated

to do, to try and reconstruct the present invention through hindsight.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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